AR201-13361

The Plastics Industry Trade Association

December 7, 2001

Christine Todd Whitman, Administrator
U. S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

Attention: Chemical Right-to-Know

RE: Test Plans and Robust Summaries for Alkyl (C_{12}-C_{14}) Glycidyl Ether (CAS No. 68609-97-2) and n-Butyl Glycidyl Ether (CAS No. 2426-08-6)

Dear Ms. Whitman:

The Society of the Plastics Industry, Inc. (SPI), on behalf of its Epoxy Resin Systems Task Group (ERSTG), is pleased to submit the Alkyl (C_{12}-C_{14}) Glycidyl Ether and n-Butyl Glycidyl Ether Test Plans and Robust Summaries under our commitment to the U. S. High Production Volume (HPV) Challenge Program.

We understand this information will be posted on the internet for a 120-day comment period after EPA's initial review, and that the ERSTG will have an opportunity to respond to all comments generated by or provided to EPA. Please contact me at 202-974-5217 or e-mail me at lharris@socplas.org to forward comments, if you have further questions or require additional information.

Sincerely,

Lynne R. Harris
Executive Director
Epoxy Resin Systems Task Group

cc w/o attachments: C. Auer, EPA
R. Hefter, EPA
O. Hernandez, EPA
B. Leczynski, EPA
R. Northrop, EPA
F. McEldowney, American Chemistry Council

Attachments

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MR-53386

AR201-13351A

High Production Volume (HPV) Challenge Program

Test Plan and Robust Summaries

For

Alkyl (C_{12}-C_{14}) Glycidyl Ether

Submitted to the US Environmental Protection Agency

by

Epoxy Resin Systems Task Group (ERSTG)
The Society of the Plastics Industry, Inc. (SPI)
1801 K Street, NW, Suite 600K
Washington, D.C. 20006

December 2001

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1.0 INTRODUCTION

Alkyl glycidyl ethers (AGEs) are epoxy resin additives derived from glycidol and are used as modifiers for other epoxides in flooring and adhesives. The TSCA Section 4 Interagency Testing Committee (ITC) designated the category glycidol and its derivatives (termed 'glycidyls') for priority consideration for health effects testing. The chemical category, glycidyls, was defined by the Environmental Protection Agency's (EPA) ITC as all substances with the general formula:

$R\text{-}O\text{-}CH_2CH(O)CH_2$

where R is a hydrogen atom or any alkyl, aryl, or acyl group, and R is unrestricted as to the number and type of substituents it may carry.

The Epoxy Resin Systems Task Group (ERSTG) has committed to provide basic chemistry, environmental fate, ecotoxicity and human health effects information on alkyl (C_{12}-C_{14}) glycidyl ether (CAS 68609-97-2) listed under the EPA High Production Volume (HPV) Chemical Challenge Program. By participating in this voluntary program, the ERSTG has agreed to assess the adequacy of existing data; prepare summaries of the data characterizing the chemical; determine data needed to fulfill the HPV data requirements; and design and submit a test plan to satisfy these testing requirements.

The HPV Challenge Program endorses the development of chemical categories and the use of surrogate data from a structurally similar chemical(s) as an acceptable mechanism to achieve an efficient completion of the program goals. EPA considers this an acceptable premise for chemicals whose physicochemical and toxicological properties are likely to be similar, or follow a regular pattern as a result of structural similarity. In this context, EPA and certain alkyl glycidyl ether manufacturers negotiated an Enforceable Consent Agreement (ECA) (Docket: OPPTS-42185, FR, March 22, 1996) wherein these companies agreed to perform certain health effects tests using alkyl (C_{12}-C_{13}) glycidyl ether (CAS # 120547-52-6) as a representative of the alkyl glycidyl ether subcategory of EPA's test rule for glycidol and its derivatives. This includes the HPV chemical alkyl (C_{12}-C_{14}) glycidyl ether. Many of these health effects tests have been completed, submitted to EPA, and are reviewed herein under Health Effects Data. In light of this agreement, and structural similarities, the ERSTG believes alkyl (C_{12}-C_{13}) glycidyl ether is an acceptable surrogate source of data in support of alkyl (C_{12}-C_{14}) glycidyl ether under the HPV Challenge Program.

2.0 EVALUATION OF DATA

When and where data are lacking for the HPV chemical, alkyl (C_{12}-C_{14}) glycidyl ether, use of data from the surrogate chemical, alkyl (C_{12}-C_{13}) glycidyl ether is not only scientifically justified, but also encouraged. This position is bolstered by: (1) EPA's guidance on this particular category (i.e. glycidyls) noted above under 1.0; and (2) its position presented before the OECD Working Party on Existing Chemicals (1999) that industry should minimize, as well as optimize, animal usage when fulfilling HPV data

requirements. Therefore, data for both CAS # 120547-52-6 and 68609-97-2 have been considered equally with regards to HPV data requirements for CAS #68609-97-2, using scientifically reliable data. A table showing the available studies for the HPV endpoints is located on page 7.

2.1 Physical Chemical Description of Alkyl (C_{12}-C_{14}) Glycidyl Ether

2.1.1 Melting Point: 35°F [Ref 9]

2.1.2 Boiling Point: 420°F [Ref 10]

2.1.3 Vapor Pressure: 0.06 mmHg @ 70°F [Ref 11]

2.1.4 Partition Coefficient: No data

2.1.5 Water Solubility: 0.01444 mg/L [Ref 12]

2.1.6 Summary of Physical/Chemical Data

Data are available for all alkyl (C_{12}–C_{14}) glycidyl ether physical chemical endpoints except the partition coefficient. Testing is proposed to determine the partition coefficient of alkyl (C_{12}–C_{14}) glycidyl ether.

2.2 Environmental Fate and Pathways Data

2.2.1 Biodegradation

No data available; testing is proposed to determine biodegradation.

2.2.2 Photodegradation

Estimation Programs Interface for Microsoft® Windows (EPIWIN V3.05, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, D.C.), Atmospheric Oxidation Program (v1.90) modeling component was used to calculate the rate of photodegradation for alkyl (C_{12}–C_{14}) glycidyl ether. The half-life was calculated to be 0.331 days (or 3.97 hours), assuming the reaction occurred over a 12-hour day with an average atmospheric concentration of 1.5E6 OH/cm^3. [Ref. (13)]

2.2.3 Hydrolysis (Stability in Water)

No data available; testing is proposed to determine stability in water.

2.2.4 Transport/Distribution

The LEV3EPI fugacity model (from EPIWIN V3.05, USEPA) was used for predicting partitioning of alkyl (C_{12}–C_{14}) glycidyl ether among air, water, soil and sediment compartments. The following are the concentration results using a soil K_{oc} of 7.29e+006 as calculated by the model and a log K_{ow} of 7.25 as calculated by the KOWWIN (USEPA) program [Ref. (14)]:

- Air 0.6%
- Water 7.7%
- Soil 28.8%
- Sediment 62.9%

2.2.5 Summary of Environmental Fate and Pathways Data

The photodegradation and fugacity of alkyl (C_{12}–C_{14}) glycidyl ether were assessed through computer modeling. Biodegradability and hydrolysis data are not available for alkyl (C_{12}–C_{14}) glycidyl ether. Testing is proposed to determine the biodegradability of alkyl (C_{12}–C_{14}) glycidyl ether and its stability in water.

2.3 Ecotoxicology Data

No Ecotoxicology data is available for alkyl (C_{12}–C_{14}) glycidyl ether. The following ecotoxicology testing is therefore proposed: acute toxicity to fish, acute toxicity to aquatic invertebrates and toxicity to aquatic plants.

2.4 Health Effects Data

2.4.1 Acute Health Effects

2.4.1.1 Acute Dermal Toxicity

Sexually mature male New Zealand albino rabbits were exposed dermally to doses of alkyl (C_{12}-C_{14}) glycidyl ether, ranging from 0.5 to 4.5 ml/kg (equivalent to 4 g/kg). The test material was applied undiluted. There was no mortality. Only slight irritation was observed at 24 hours, and moderate irritation was reported after 72 hours in all treated groups. Immediately prior to sacrifice, blood was collected from the vena cava of each animal and checked for Hgb, Hct, WBC, RBC, and differential leukocyte counts. Organ weights were determined for testes with and without epididymis, and for liver, heart, kidneys and brain. The testes, epididymis, ductus deferens, seminal vesicles, prostate and heart were further subjected to histopathological examination. There were no compound-related effects on body weight, organ weights, and blood morphology, and no adverse effects observed at gross necropsy or histopathological examinations. [Ref. (8)]

2.4.1.2 Summary of Acute Toxicological Effects

Alkyl (C_{12}-C_{14}) glycidyl ether demonstrated a dermal LD50 of >4 g/kg body weight, causing only slight to moderate irritation after 3 days. Further examination of selected organs and blood parameters failed to illustrate any adverse effects on the blood parameters measured or tissues examined. Special attention was given to the male reproductive organs, as well as liver and kidneys. This dermal toxicity test satisfies the HPV requirement for acute health effects data. No further acute toxicity testing is proposed.

2.4.2 Genetic Toxicology

2.4.2.1 Bacterial Gene Mutation Assay

Alkyl (C_{12}-C_{13}) glycidyl ether was examined in a contemporary bacterial reverse mutation assay using Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and Escherichia coli strain WP2 uvrA in the presence or absence of Aroclor 1254-induced rat liver S9. Alkyl (C_{12}-C_{13}) glycidyl ether was mutagenic in Salmonella typhimurium TA1535 with and without S9 activation. [Ref. (4)]

2.4.2.2 In Vitro Mammalian Cell Gene Mutation Assay

Alkyl (C_{12}-C_{13}) glycidyl ether was tested in the Chinese hamster ovary (CHO) cells, subline CHO-K_1-BH_4, in the presence and absence of Aroclor 1254-induced rat liver S9. In a preliminary cytotoxicity assay, alkyl (C_{12}-C_{13}) glycidyl ether produced a visible precipitate at 500 µg/ml and above, when tested at doses of 0.5 to 5000 µg/ml with and without activation. Cloning efficiency was 18% at 5000 µg/ml without activation, and 4% at 150 µg/ml with metabolic activation. Based upon the toxicity test results the doses selected ranged from 100-5000 µg/ml without activation, and 25-150 µg/ml with S9 activation. The minimum mutation frequency was set at >40 mutants per 10^6 clonable cells. Alkyl (C_{12}-C_{13}) glycidyl ether did not induce mutations at the HGPRT locus in Chinese hamster ovary cells. [Ref. (6)]

2.4.2.3 In Vivo Chromosomal Aberration Assay

Alkyl (C_{12}-C_{13}) glycidyl ether was examined for chromosomal aberration effects in a micronucleus cytogenetic assay using ICR mice. The test material was given via intraperitoneal injection at doses up to 4000 mg/kg determined from a preliminary pilot toxicity assay. The number of micronucleated polychromatic erythrocytes (PCEs) per 1000 erythrocyte cells in the test groups was not statistically increased relative to the vehicle control in either sex. Alkyl (C_{12}-C_{13}) glycidyl ether was not clastogenic in the micronucleus test using male and female ICR mice. [Ref. (5)]

2.4.2.4 Summary of Genetic Toxicology Effects

Alkyl (C_{12}-C_{13}) glycidyl ether was examined for gene mutations in in vitro bacteria and mammalian cell assays. Alkyl (C_{12}-C_{13}) glycidyl ether was positive for basepair substitutions in Salmonella typhimurium strain TA1535 in the bacterial reverse mutation assay. However, it was negative in all other Salmonella typhimurium strains tested (TA98, TA100 and TA1537), as well as E. coli strain WP2 uvrA. E. coli WP2 uvrA and Salmonella typhimurium TA 100, which also test for basepair substitutions, were negative. In an in vitro cytogenetic assay in mammalian cells in culture (CHO- K_1-BH_4), alkyl (C_{12}-C_{13}) glycidyl ether was negative.

Alkyl (C_{12}-C_{13}) glycidyl ether was not clastogenic when examined for in vivo chromosomal aberrations in the micronucleus assay using ICR mice. Alkyl (C_{12}-C_{13}) glycidyl ether was not genotoxic in mammalian assays that measured gene mutations and chromosomal aberrations. The results of these genetic toxicity assays satisfy the HPV requirements for genetic toxicity data and no further genetic toxicity testing is recommended.

2.4.3 Repeated Dose Health Effects

2.4.3.1 Subchronic Dermal Toxicity

Alkyl (C_{12}-C_{13}) glycidyl ether was administered dermally once a day, 5 days/week for 14 days to male and female Fischer 344 rats in 2-week range-finding study. Doses ranged from 10-1000 mg/kg/day. Doses of 1000 mg/kg exceeded the maximum tolerated dose. Epidermal hyperplasia of the sebaceous glands was present at 100 and 1000 mg/kg. Dermal changes at 10 mg/kg were limited to slight scaling. [Ref. (1)]

In a 13-week repeated dose dermal toxicity study, Fischer 344 rats were exposed to doses of alkyl (C_{12}-C_{13}) glycidyl ether once/day, 5 days/week for 13 weeks. A total of 66 daily doses were administered, ranging from 1 to 100 mg/kg. Test material was not occluded or wiped off between doses. Cageside observations conducted daily were unremarkable. Food consumption and body weight gain were not affected. There were no compound-related effects on hematological, clinical chemistry, or urinalysis parameters measured. There was also no effect on organ weights for adrenal glands, liver, kidneys, brain, ovaries and testes. A full compliment of tissues were fixed and examined grossly, including all reproductive organs in control and high-dose groups. No adverse effects were observed except for thickened and scaly skin in high-dose rats at the site of application. Histopathological evaluation of tissues revealed only effects to the dermis in high-dose rats, with hyperkeratosis and hyperplasia of the epidermis, hyperplasia of sebaceous glands and inflammation. A No Observable Adverse Effect Level (NOAEL) was demonstrated at 1 mg/kg, based upon effects on the skin at 10 and 100 mg/kg. [Ref. (2)]

A 13-week neurotoxicity study was performed using Fischer 344 rats. They were exposed to repeated dermal doses (1 to 100 mg/kg) of alkyl (C_{12}-C_{13}) glycidyl ether once/day, 5days/week for 14 weeks. Test material was not occluded or wiped off between doses. Cageside observations conducted daily were unremarkable. Body weight gain was not affected. Dermal effects were confined to the mid- and high- dose groups, with well-defined erythema, edema, and moderate to severe scabbing. Effects were more severe in the high-dose rats, compared to mid-dose animals. No compound-related effects were seen in control or low-dose animals. Functional Observational Battery (FOB) and Motor Activity (MA) analyses were conducted pre-exposure and at the end of each month of exposure. There were also Electrodiagnostic Tests or Evoked Potential Battery conducted within a few days of the last exposure, plus a comprehensive neuropathological examination of perfused tissues. Histological examination was confined to neuropathology of the CNS and PNS in high-dose and control groups only. There were no effects observed for FOB, MA or for neuropathology. Electroretinograms (ERGs) were performed to identify effects on the retina. These were followed by histopathological examination of the retinas to confirm structural changes. No adverse effects were observed or confirmed, and it was concluded that a NOAEL of 1 mg/kg was demonstrated, based upon effects on the skin at 10 and 100 mg/kg, and mild Flash Evoked Potential (FEP) alterations in male rats at 10 and 100 mg/kg. [Ref. (3)]

Based upon the data generated from these contemporary repeated dose studies, conducted under Good Laboratory Practice (GLP) regulations, and in recognition of the testing requirements in the ECA, no additional repeated dose studies are proposed.

2.4.4 Reproductive Toxicity

Effects on the reproductive organs were assessed in several separate toxicity studies summarized above. The male reproductive organs were examined histologically in the acute dermal LD50 study (2.4.1.1) using alkyl (C_{12}-C_{14}) glycidyl ether and no effects observed at doses up to 4 g/kg. Gross necropsy of male and female Fischer 344 rats exposed for 2 weeks to dermal doses of alkyl (C_{12}-C_{13}) glycidyl ether of up to 100 mg/kg

revealed no adverse effects. In a 13-week dermal study, also in Fischer 344 rats, gross and histopathologic examinations revealed no adverse effects on the ovaries and testes of animals dosed with alkyl (C_{12}-C_{13}) glycidyl ether at 100 mg/kg. In a separate 13-week neurotoxicity study using alkyl (C_{12}-C_{13}) glycidyl ether, which included FOB and EP tests, there were no adverse effects on the reproductive organs in male and female rats examined grossly at doses up to and including 100 mg/kg. [Ref. (2) and (3)]

Based upon these findings and the results from a developmental toxicity study, no further testing for reproductive effects is recommended. This conclusion is supported by guidance presented in EPA's guidance document for meeting HPV testing requirements wherein it is recommended that when a scientifically reliable 90-day repeated dose study also examines the reproductive organs, a separate reproductive toxicity study is not necessary. Further, when effects on reproductive organs are examined in a 90-day study and where there is also an adequate developmental study, the HPV requirement for a reproductive study is satisfied.

2.4.5 Developmental Toxicity

Virgin female Sprague-Dawley rats were mated with resident male rats of the same strain, and, after confirmation of pregnancy, were given alkyl (C_{12}-C_{13}) glycidyl ether dermally, 6 hours per day from gestation day 6 thru 15. There were 5 dose levels administered, ranging from 1 to 200 mg/kg. Dermal sites were not occluded and test material was removed by washing after each 6-hour exposure period. Females were sacrificed on day 20 of gestation. There were no significant cageside observations, no effect on body weight gain or food consumption and no adverse autopsy findings. The only adverse effect observed was dermal irritation at 50 mg/kg and greater. Fissuring, eschar formation, and atonia occurred at 100 and 200 mg/kg. The NOAEL for dermal irritation was 10 mg/kg. There were no compound related effects on fertility, intrauterine growth, survival, the number of CL, implantation sites, early or late resorptions, or on the number of dead fetuses. Mean fetal crown-rump length, mean placenta weight, and mean fetal body weight were similar in all groups. There were no external malformations or developmental variations observed and a NOAEL of 200 mg/kg was determined in this study for maternal and developmental toxicity. [Ref. (7)]

The study was conducted in accordance with a recognized scientific procedure and screening bioassay for examining compound related effects on the developing fetus and in compliance with GLP regulations. No further developmental testing is proposed.

2.4.6 Summary of Repeated Dose, Reproductive and Developmental Toxicity Effects

All of the repeated dose and developmental toxicity studies were performed using alkyl (C_{12}-C_{13}) glycidyl ether, as agreed in the ECA. All studies are considered scientifically reliable and support the findings with respect to NOAELs and compound related effects observed. Repeated dermal contact for 2 weeks or 13 weeks resulted in a NOAEL of 1 mg/kg/day.

Potential neurological effects were evaluated in rats following repeated dermal exposures for 14 weeks. A NOAEL of 1 mg/kg was demonstrated, based upon effects on the skin at 10 and 100 mg/kg, and mild Flash Evoked Potential (FEP) alterations in male rats at 10 and 100 mg/kg.

Effects on the reproductive organs were assessed in all of the repeated dose studies summarized above. There were no adverse effects on the reproductive organs in males and females examined grossly or histologically at doses up to and including 100 mg/kg.

In a separate dermal developmental screening study, there were no compound related effects and a NOAEL of 200 mg/kg was determined for maternal and developmental toxicity.

All of these studies are scientifically reliable, comply with GLP regulations and were conducted according to international standards for such studies. No further repeated dose, reproductive or developmental toxicity testing is proposed.

3.0 CONCLUSIONS

The following table identifies the data available and the data gaps which exist for alkyl (C_{12}-C_{14}) glycidyl ether. Partition coefficient data will be generated, as will stability in water and biodegradation. Also, the following ecotoxicity tests will be conducted, as appropriate: acute toxicity to fish, acute toxicity to aquatic invertebrates, and toxicity to aquatic plants.

Based upon the examination of available health effects data it is proposed that no further health effects studies or data are needed. All health effects studies fulfilling HPV data requirements are scientifically reliable, comply with GLP regulations and were conducted according to international standards for such studies.

TABLE 1: HPV DATA REQUIREMENTS/CRITICAL STUDIES: Alkyl (C_{12}-C_{14}) Glycidyl Ether

HPV Data Category	Test Endpoint		Data Acceptable	Data to be Generated
Physical and Chemical Properties	Melting Point		Yes	No
	Boiling Point		Yes	No
	Vapor Pressure		Yes	No
	Partition Coefficient		ND	Yes
	Water Solubility		Yes	No
Environmental Fate and Pathways	Photodegradation		Yes	No
	Stability in Water		ND	Yes
	Biodegradation		ND	Yes
	Transport/Distribution		Yes	No
Ecotoxicity	Acute toxicity to Fish		ND	Yes
	Acute toxicity to Aquatic Invertebrates		ND	Yes
	Toxicity to Aquatic Plants		ND	Yes
	Chronic aquatic invertebrate test[1]		NR	No
	Terrestrial toxicity[1]		NR	No
Health Effects	Acute toxicity		AD-1 (2)	No
	Repeated Dose		SC-4, -5 and –6 (1) SU	No
	Genetic Toxicity	Gene Mutation	MU-17 and –19 (1) SU	No
		Chromosome Aberration	MU-18 (1) SU	No
	Reproductive Toxicity		SC-5 and –6 (1) SU	No
	Developmental Toxicity		DE-1 (2) SU	No

1 = Test are not required for all chemicals; only when appropriate.
NR = Not required
ND = No Data
SU = Surrogate Data (EPA Enforceable Consent Agreement; C12-C13)

Data listed are cross-referenced to a Robust Summary Report number (i.e. AD-1 (2)); which identifies the report number and Klimisch Rating in ( ). Only studies with the following Klimisch Ratings are included: (1) = reliable without restriction and (2) = reliable with restriction. If this is followed by SU it means the critical study (s) was (were) derived from surrogate data (i.e. C_{12}-C_{13}). If more than one study is listed it means they are co-critical.

LIST OF REFERENCES

120547-52-6 (C_{12}-C_{13})

Ref.(1). SC-4 (C_{13}): Repeated Dose
The Society of the Plastics Industry, Epoxy Resin Systems C_{12}-C_{14} Task Force. Alkyl Glycidyl Ether: 2-Week Range Finding and 13-Week Repeated Dose Dermal Toxicity Study in Fischer 344 Rats. Testing Facility: Toxicology Research Laboratory, Health & Environmental Research Laboratories, Dow Chemical USA, Midland MI; Study #960026; Study dated August 1997.
Klimisch = 1

Ref.(2). SC-5 (C_{13}): Repeated Dose and Reproduction
The Society of the Plastics Industry, Epoxy Resin Systems C_{12}-C_{14} Task Force. Alkyl Glycidyl Ether: 2-Week Range Finding and 13-Week Repeated Dose Dermal Toxicity Study in Fischer 344 Rats. Testing Facility: Toxicology Research Laboratory, Health & Environmental Research Laboratories, Dow Chemical USA, Midland MI; Study #960026; Study dated August 1997.
Klimisch = 1

Ref.(3). SC-6 (C_{13}): Repeated Dose and Reproduction
The Society of the Plastics Industry, Epoxy Resin Systems C_{12}-C_{14} Task Force. Alkyl Glycidyl Ether: 13-Week Neurotoxicity Study in Fischer 344 Rats. Testing Facility: Toxicology Research Laboratory, Health & Environmental Research Laboratories, Dow Chemical USA, Midland MI; Study #971000 PTR#50068-240-1; Study dated November 1997.
Klimisch = 1

Ref.(4). MU-17 (C_{13}): In Vitro (Gene Mutation: Bacteria)
The Society of the Plastics Industry, Epoxy Resin Systems C_{12}-C_{14} Task Force. Bacterial Reverse Mutation Assay with an Independent Repeat Assay. Testing Facility: MA BioServices, Inc., 9630 Medical Center Drive, Rockville, MD 20850; Study # G96BK39.502001R; Project 805-13-2; Study dated November 1997.
Klimisch = 1

Ref.(5). MU-18 (C_{13}): In Vivo (Chromosomal Aberration)
The Society of the Plastics Industry, Epoxy Resin Systems C_{12}-C_{14} Task Force. Micronucleus Cytogenetic Assay in Mice. Testing Facility: Microbiological Associates, Inc. (MA), 9630 Medical Center Drive, Rockville, MD 20850; Study #G96BK39.122; Project 805-13-3; Study dated February 1997.
Klimisch = 1

Ref.(6). MU-19 (C_{13}): In Vitro (Gene Mutation: Mammalian Cell)
The Society of the Plastics Industry, Epoxy Resin Systems C_{12}-C_{14} Task Force. In Vitro Mammalian Cell Gene Mutation Test with an Independent Repeat Assay. Testing Facility: MA BioServices, Inc., 9630 Medical Center Drive, Rockville, MD 20850; Study # G96BK39.782001R; Project 805-13-2; Study dated March 1998.
Klimisch = 1

Ref.(7). DE-1 (C_{13}): Developmental
The Society of the Plastics Industry, Epoxy Resin Systems C_{12}-C_{14} Task Force. A Dermal Developmental Toxicity Screening Study of Alkyl Glycidyl Ether in Rats. Testing Facility: WIL Research Laboratories, Ashland, OH 44805-9281; Study #WIL-284001; Study dated August 1996.
Klimisch = 2

68609-97-2 (C_{12}-C_{14})

Ref.(8). AD-1 (E): Acute Dermal
The Proctor and Gamble Company. Multi-Dose Acute Percutaneous Toxicity - Rabbits. Testing Facility: Springborn Institute for Bioresearch, Inc. Spencerville, OH 45887; Study #3029.526; Study dated April 1980.
Klimisch = 2

Ref.(9). Melting Point
Powell, C. H. (ed). *Patty's Toxicology*. John Wiley & Sons, Inc., 2001.
Klimisch = 2

Ref.(10). Boiling Point
Powell, C. H. (ed). *Patty's Toxicology*. John Wiley & Sons, Inc., 2001.
Klimisch = 2

Ref.(11). Vapor Pressure
Powell, C. H. (ed). *Patty's Toxicology*. John Wiley & Sons, Inc., 2001.
Klimisch = 2

Ref.(12). Water Solubility
Estimation Programs Interface for Microsoft® Windows (EPIWIN V3.05, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, D.C.)
Klimisch = 2

Ref. (13). PD-1: Photodegradation
Estimation Programs Interface for Microsoft® Windows (EPIWIN V3.05, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, D.C.)
Klimisch = 2

Ref. (14) TD-1: Transport/Distribution
Estimation Programs Interface for Microsoft® Windows (EPIWIN V3.05, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, D.C.)
Klimisch = 2

AR201-13351B

ENVIRONMENTAL FATE/PATHWAYS: ROBUST SUMMARIES

PHOTODEGRADATION

REPORT NUMBER: PD-1

STUDY TYPE: Photodegradation

TEST MATERIAL: Alkyl (C_{12}-C_{14}) glycidyl ether

STUDY NUMBER(S): Not applicable

SPONSOR: Air Products and Chemicals, Inc.

TESTING FACILITY: Air Products and Chemicals, Inc.

TITLE OF REPORT: Not applicable

AUTHOR(S): Not applicable

REPORT ISSUED or COMPLETION DATE: August 23, 2001

RECOGNIZED METHOD, i.e OECD: Modeling conducted; no guideline studies used.

GLP: Not utilized

METHOD: Estimation Programs Interface for Microsoft® Windows (EPIWIN V3.05, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, D.C.), Atmospheric Oxidation Program (v1.90) modeling component. Model executed in August 2001.

RESULTS/OBSERVATIONS: The AOP component of EPIWIN was used to calculate the rate of photodegradation for alkyl (C_{12}-C_{14}) glycidyl ether. Results suggest alkyl (C_{12}-C_{14}) glycidyl ether readily absorbs solar radiation and undergoes photochemical degradation; the half-life was calculated to be 0.331 days (or 3.97 hours). This assumes the reaction occurred over a 12-hour day with an average atmospheric concentration of 1.5E6 OH/cm^3.

DATA QUALITY: Data was generated by a scientific model based on structure-activity relationships that are well documented and acceptable for use in environmental assessments.

RELIABILITY:

1 w/o restriction	[ ]
2 w restriction	[X]
3 not reliable	[ ]
4 not assignable	[ ]

Reason for Reliability Code: Reference is a scientific model.

TRANSPORT/DISTRIBUTION (FUGACITY)

REPORT NUMBER: TD-1

STUDY TYPE: Transport/distribution between environmental compartments (fugacity)

TEST MATERIAL: Alkyl (C_{12}-C_{14}) glycidyl ether

STUDY NUMBER(S): Not applicable

SPONSOR: Air Products and Chemicals, Inc.

TESTING FACILITY: Air Products and Chemicals, Inc.

TITLE OF REPORT: Not applicable

AUTHOR(S): Not applicable

REPORT ISSUED or COMPLETION DATE: August 23, 2001

RECOGNIZED METHOD, i.e OECD: Modeling conducted; no guideline studies used.

GLP: Not utilized

METHOD: Estimation Programs Interface for Microsoft® Windows (EPIWIN V3.05, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, D.C.), LEV3EPI fugacity model used to predict partitioning among air, water, sediment and soil. Model executed in August 2001.

RESULTS/OBSERVATIONS: The following are the results from the LEV3EPI model for predicting partitioning of alkyl (C_{12}-C_{14}) glycidyl ether among air, water, soil and sediment. Results were obtained by running a single level III output using the LEV3EPI model default emission rates of 1000 kg/hr for air, water and soil. The advection times used were also the LEV3EPI model default values. The half-life values used were those calculated by BIOWIN and AOPWIN programs. The LEV3EPI model used the experimental log Kow value from the KOWWIN program to calculate the soil Koc value.

Level III Fugacity Model (Full-Output):
Chem Name: Oxirane, mono[(C_{12}-C_{14})-alkyloxy)methyl] derivs.
Molecular Wt: 254.46 g/mol
Henry's LC: 0.0112 atm-m3/mole (Henrywin program)
Vapor Press: 0.00105 mm Hg (Mpbpwin program)
Liquid VP: 0.00222 mm Hg (Mpbpwin program)
Melting Pt: 57.9 deg C (Mpbpwin program)
Log Kow: 7.25 (Kowwin program)

Soil Koc: 7.29e+006 (calc by model)

LEV3EPI Compartmental Distribution from EPIWIN V3.05 Fugacity Calculation

Media		LEV3EPI Default Values	
	Half-Life (hr)	Emissions (kg/hr)	Concentration, Percent
Air	7.94	1000	0.585
Water	360	1000	7.69
Soil	360	1000	28.8
Sediment	1.44e+003	0	62.9

Data From LEV3EPI Default Input Emissions

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	1.01e-011	921	105	30.7	3.52
Water	2.38e-009	267	139	8.89	4.62
Soil	7.26e-012	1e-003	0	33.3	0
Sediment	7.13e-010	546	22.7	18.2	0.756

	LEV3EPI Default
Persistence Time:	601 hr
Reaction Time:	659 hr
Advection Time:	6.76e+003 hr
Percent Reacted:	91.1
Percent Advected:	8.89

Half-Lives (hr) (based upon BIOWIN [Ultimate] and AOPWIN):
Air: 7.939
Water: 360
Soil: 360
Sediment: 1440
BIOWIN estimate: 2.927 (weeks)

Advection Times (hr) (based on LEV3EPI default values):
Air: 100
Water: 1000
Sediment: 5e+004

DATA QUALITY: EPIWIN V3.05 data are predictive estimates from LEV3EPI model developed by the EPA Office of Pollution Prevention and Toxics and Syracuse Research

Corporation. Estimates from the model are reliable for estimating partitioning among environmental compartments based on the input parameters.

RELIABILITY:

1 w/o restriction	[ ]
2 w restriction	[X]
3 not reliable	[ ]
4 not assignable	[ ]

Reason for Reliability Code: Reference is a scientific model.

CHEMICAL: Alkyl (C_{12}-C_{13}) glycidyl ether;CAS # 120547-52-6

HEALTH EFFECTS (TOXICITY) TESTS: ROBUST SUMMARIES

REPEATED DOSE (Subchronic) TOXICITY

TOXICITY REPORT NUMBER: SC-4 (C_{13})

STUDY TYPE: 2-Week Range Finding Repeated Dose Dermal Toxicity Study

TEST MATERIAL: Alkyl (C_{12}-C_{13}) Glycidyl Ether; clear colorless liquid; purity >98%; 49.07% n-dodecyl glycidyl ether (C_{12}) and 39.31% n-tridecyl glycidyl ether (C_{13}); stability in acetone determined and homogeneity in solution measured.

STUDY NUMBER(S): 960026

SPONSOR: The Society of the Plastics Industry, Epoxy Resin Systems C_{12}-C_{14} Task Force

TESTING FACILITY: Toxicology Research Laboratory, Health & Environmental Research Laboratories, Dow Chemical USA, Midland, MI

TITLE OF REPORT: Alkyl Glycidyl Ether: 2-Week Range Finding and 13-Week Repeated Dose Dermal Toxicity Study in Fischer 344 Rats

AUTHOR(S): R.J. McGuirk and K.A. Johnson

REPORT ISSUED or STUDY COMPLETION DATE: August 18, 1997

RECOGNIZED METHOD, i.e. OECD: OECD 410 for 21/28-Day Repeated Dose Dermal Toxicity Study.

GLP: Yes

SPECIES/SEX: Male and female Fischer 344 rats from Charles River Breeding Laboratories.

AGE at Start of Test: Eight weeks old at the start of the study.

ROUTE: Dermal; percutaneous.

DURATION OF TEST: Fourteen days (10 exposures); doses were administered once per day, five days/week. Hourly exposure was not relevant as the test material was not occluded and not wiped off after a certain time or before the next application.

DOSE LEVEL(s) and NUMBER OF DOSES: All animals were exposed to 0, 10, 100 or 1000 mg/kg/day. Test material was administered dilute in acetone. Animals in high dose group were sacrificed after the fourth application due to the loss of integrity of the epidermis.

NUMBER OF ANIMALS/DOSE: Two males, two females per dose.

VEHICLE: Acetone.

BODY WEIGHT MEASUREMENTS: Not determined in the range-finding study.

FOOD CONSUMPTION/FOOD EFFICIENCY: Not measured.

HEMATOLOGY: Not measured.

CLINICAL CHEMISTRY: Not measured.

URINALYSIS: Not measured.

STATISTICAL METHODS: Not performed.

ORGAN WEIGHTS: Not measured.

GROSS PATHOLOGY: Full compliment of tissues were fixed and examined. Most significant treatment related effects occurred to the integrity of the dermis at 100 and 1000 mg/kg; epidermal hyperplasia of the sebaceous glands was present in both groups; most severe effects in 100 and 1000 mg/kg groups with erythema, edema, scaling, and fissuring; scab formation increased in severity resulting in the early sacrifice of the high dose group animals. Dermal changes at 10 mg/kg were limited to slight scaling.

FINDINGS/MEASURED ENDPOINT/INDEX (i.e. LOEL, NOAEL): Four daily doses of 1000 mg/kg exceeded the maximum tolerated dose. A NOAEL was not demonstrated due to the dermal effects at all dose levels.

DATA QUALITY: Study was conducted in accordance with a recognized range-finding procedure for assessing dose levels for evaluation in a longer term, 90-day repeated dose dermal toxicity test. The study succeeded in determining a range of effective doses to use in a 90-day study. The study was conducted in compliance with GLP regulations and provides full characterization of the test material.

RELIABILITY:

1 w/o restriction	[X]
2 w restriction	[ ]
3 not reliable	[ ]
4 not assignable	[ ]

Reason: Followed recognized toxicology testing procedures and test material adequately characterized.

TOXICITY REPORT NUMBER: SC-5 (C_{13})

STUDY TYPE: 13-Week Repeated Dose Dermal Toxicity Study

TEST MATERIAL: Alkyl (C_{12}-C_{13}) Glycidyl Ether; clear colorless liquid; purity >98%; 49.07% n-dodecyl glycidyl ether (C_{12}) and 39.31% n-tridecyl glycidyl ether (C_{13}); stability in acetone determined and homogeneity in solution measured.

STUDY NUMBER(S): 960026

SPONSOR: The Society of the Plastics Industry, Epoxy Resin Systems C_{12}-C_{14} Task Force

TESTING FACILITY: Toxicology Research Laboratory, Health & Environmental Research Laboratories, Dow Chemical USA, Midland, MI

TITLE OF REPORT: Alkyl Glycidyl Ether: 2-Week Range Finding and 13-Week Repeated Dose Dermal Toxicity Study in Fischer 344 Rats

AUTHOR(S): R.J. McGuirk and K.A. Johnson

REPORT ISSUED or STUDY COMPLETION DATE: August 18, 1997

RECOGNIZED METHOD, i.e. OECD: OECD 411 for 90-Day Repeated Dose Dermal Toxicity Study.

GLP: Yes

SPECIES/SEX: Male and female Fischer 344 rats from Charles River Breeding Laboratories.

AGE at Start of Test: Eight weeks old at the start of the study.

ROUTE: Dermal; percutaneous.

DURATION OF TEST: Thirteen weeks (66 exposures); doses were administered once per day, five days/week for 13 weeks. Hourly exposure was not relevant as the test material was not occluded and not wiped off after a certain time or before the next application.

DOSE LEVEL(s) and NUMBER OF DOSES: All animals were exposed to 0, 1, 10 or 100 mg/kg/day. Test material was administered dilute in acetone.

NUMBER OF ANIMALS/DOSE: Ten males, ten females per dose.

VEHICLE: Acetone.

CAGESIDE OBSERVATIONS: Examined daily for integrity of the skin, fur, mucous membranes, respiration, nervous system function (tremors, convulsions), swelling, masses and general behavior. There were no compound related effects observed.

OTHER: Dermal test site was scored daily prior to application for the first week, then weekly thereafter for 13 weeks. Dermal effects were confined to the mid and high dose groups, with slight to moderate edema, slight to well-defined erythema and slight fissuring.

BODY WEIGHT MEASUREMENTS: Measured during predosing and weekly thereafter. There were no compound related changes in body weights.

FOOD CONSUMPTION/FOOD EFFICIENCY: Measured weekly during dosing. Based upon one rat per cage but determined by group means. There were no compound related changes in food consumption.

HEMATOLOGY: Determined in all animals from the orbital sinus at predosing, 30 days and after 13 weeks. Hematological measurements included: rbc, wbc count and morphology, differential counts, platelet count and morphology, Hgb concentration, and hematocrit. There were no compound related changes in hematological measurements.

CLINICAL CHEMISTRY: Determined in all animals from orbital sinus at predosing, 30 days and after 13 weeks. Clinical chemistry measurements included: AP, alanine aminotransferase, aspartate aminotransferase, creatine phosphokinase, BUN, creatinine, total protein, albumin, globulin, glucose, total bilirubin, electrolytes, cholesterol, and triglycerides. There were no compound related changes in clinical measurements.

URINALYSIS: Obtained after one month of dosing and at 13 weeks. The following parameters were determined: specific gravity, color, appearance, microscopic exam of sediment, pH, protein, glucose, ketones, bilirubin, blood and urobilinogen. There were no compound related changes in urinary measurements.

STATISTICAL METHODS: All parameters examined statistically were first tested for equality of variance using Bartlett's test. Body weight, hematology and clinical chemistry were statistically evaluated via 3-way repeated measures of variance (ANOVA). A Bonferoni correction was applied to compensate for multiple comparisons with the control group (time-dose comparisons). Terminal body weight, organ weights (absolute and relative) and urine specific gravity were evaluated using 2-way ANOVA. Comparisons of individual dose groups to control were made with Dunnett's test. Results of ovary and testes weight (abs. and rel.) were analyzed by 1-way ANOVA; any significant differences were compared to control using Dunnett's test. Different levels of significance were used based upon the statistical comparisons employed; i.e. $p<0.01$ - 0.05.

ORGAN WEIGHTS: Absolute and relative organ weights (organ-body weight) were measured for adrenal glands, liver, kidneys, brain, ovaries and testes. There were no statistically significant differences between test groups and controls.

GROSS PATHOLOGY: Full compliment of tissues were fixed and examined, including all reproductive organs in control and high dose groups. Also, lungs, liver, kidneys, and skin were examined in mid and low dose groups as well. The only effect attributable to treatment was thickened and scaly skin at the site of application in high dose male and female rats.

HISTOPATHOLOGY: A full compliment of tissues were fixed and examined histologically in control and high dose groups, with particular attention to skin, lungs/nasal turbinates, reproductive organs. Also, lungs, liver, kidneys, and skin were examined in mid and low dose groups. Dermal sites were graded based upon findings of: epidermal hyperplasia, hyperkeratosis, parakeratosis, hyperplasia of the sebaceous glands, inflammation, ulcers, and edema. Treatment related effects were confined to the skin of high dose males and females, with hyperkeratosis and hyperplasia of the epidermis, hyperplasia of sebaceous glands, and inflammation. No adverse effects were observed in any of the reproductive organs examined.

FINDINGS/MEASURED ENDPOINT/INDEX (i.e. LOEL, NOAEL): A NOAEL was demonstrated at 1 mg/kg, based upon effects on the skin at 10 and 100 mg/kg.

DATA QUALITY: Study was conducted in accordance with recognized national and international scientific procedures for determining the toxicological effects of a test substance applied dermally repeatedly for 13 weeks in experimental animals. The study was conducted in compliance with GLP regulations, provides full characterization of the test material, and supports the finding of a NOAEL.

RELIABILITY:

1 w/o restriction	[X]
2 w restriction	[ ]
3 not reliable	[ ]
4 not assignable	[ ]

Reason: Followed recognized toxicology testing procedures and test material was adequately characterized.

TOXICITY REPORT NUMBER: SC-6 (C_{13})

STUDY TYPE: 13-Week Neurotoxicity Study in Rats

TEST MATERIAL: Alkyl (C_{12}-C_{13}) Glycidyl Ether; purity >98%; clear colorless liquid; 49.07% n-dodecyl glycidyl ether (C_{12}) and 39.31% n-tridecyl glycidyl ether (C_{13}); stability in acetone determined and homogeneity in solution measured.

STUDY NUMBER(S): 971000; PTR#50068-240-1

FOOD CONSUMPTION/FOOD EFFICIENCY: Not stated whether this was measured; however, OECD suggests that it should be measured if dosing is via food; and water consumption data are collected if dosing is via water. However, no OECD recommendation for measuring food consumption when dosing is dermal.

HEMATOLOGY: Not measured.

CLINICAL CHEMISTRY: Not determined.

URINALYSIS: Not obtained.

OTHER: Functional Observational Battery (FOB) and Motor Activity (MA) were conducted pre-exposure and at the end of each month of exposure. FOB included: Hand-held and Open-Field Observations; Grip Performance and Landing Foot Splay. Also, Electrodiagnostic tests or Evoked Potential Battery were conducted within a few days of the last exposure and included: visual pathway (Flash Evoked Potential), auditory pathway (Auditory Brainstem Response), somatosensory pathway (Somatosensory Evoked Potential), and caudal nerves (Caudal Nerve Action Potential); plus a comprehensive neuropathological examination of perfused tissues. Following EP testing after 5 weeks post-exposure, eyes and brains from all male rats were saved for possible histopathology.

STATISTICAL METHODS: Incidence of ranked FOB observations between control and each dose group (sexes separate) were evaluated by a test of proportions at a=0.02. Means and S.D. were calculated by sex for all continuous data and homogeneity of variance was evaluated with Bartlett's test (a=0.01). Initial statistical analyses were factorial repeated-measure analyses to account for data from both sexes at all time periods in one statistical analysis. Electrodiagnostic data were analyzed by ANOVA. ERG were analyzed using Wilcoxon-Mann-Whitney rank-sum statistic. The overall approach is consistent with the recommendations proposed by Tukey et al. (1985) and Mantel (1980), and by US EPA (1991).

ORGAN WEIGHTS: Organ weights not determined.

GROSS PATHOLOGY: Full compliment of tissues were fixed and examined, including all reproductive organs in 5 males and 5 females in each test and control group.

HISTOPATHOLOGY: Histological examination was confined to neuropathology of the CNS and PNS, in high dose and control groups only.

FINDINGS/MEASURED ENDPOINT/INDEX (i.e. LOEL, NOAEL): There were no significant cageside observations and no effect on body weight gain. There were no effects reported for FOB, MA, nor on neuropathology. FEPs from male mid- and high-dose rats were smaller than control, but FEPs from female high-dose rats were larger than control. Confirmatory examination included ERG of control and high-dose males; high dose ERG response was smaller than controls, suggesting a retinal effect. Histopathology of the associated retinas revealed no treatment related effects. Authors concluded that a NOAEL was demonstrated at 1 mg/kg, based upon effects on the

SPONSOR: The Society of the Plastics Industry, Epoxy Resin System C_{12}-C_{14} Task Force

TESTING FACILITY: Toxicology Research Laboratory, Health & Environmental Research Laboratories, Dow Chemical USA, Midland, MI

TITLE OF REPORT: Alkyl Glycidyl Ether: 13-Week Neurotoxicity Study in Fischer 344 Rats

AUTHOR(S): J.L. Mattsson, DVM, M.R. Shankar, P.J. Spencer, and B.L. Yano, DVM.

REPORT ISSUED or STUDY COMPLETION DATE: November 18, 1997

RECOGNIZED METHOD, i.e. OECD: OECD 411 for 90-Day Repeated Dose Dermal Toxicity Study; and OECD 424 for Neurotoxicity

GLP: Yes

SPECIES/SEX: Male and female Fischer 344 rats from Charles River Breeding Laboratories.

AGE at Start of Test: Eight weeks old at the start of the study.

ROUTE: Dermal; percutaneous.

DURATION OF TEST: Fourteen weeks; doses were administered once per day, 5 days/week for 14 weeks. Hourly exposure was not relevant as the test material was not occluded and not wiped off after a certain time or before the next application.

DOSE LEVEL(s) and NUMBER OF DOSES: All animals were exposed to 0, 1, 10 or 100 mg/kg/day. Test material was administered dilute in acetone.

NUMBER OF ANIMALS/DOSE: Twelve males, twelve females per dose.

VEHICLE: Acetone.

CAGESIDE OBSERVATIONS: Examined daily for integrity of the skin, fur, mucous membranes, respiration, nervous system function (tremors, convulsions), swelling, masses and general behavior. There were no compound related effects observed.

OTHER: Dermal test site was scored daily prior to application for the first week, then weekly thereafter for 14 weeks. Dermal effects were confined to the mid and high dose groups, with well defined erythema, edema, moderate scabbing, and moderate to severe scaling in high dose males. Female high dose rats had slight erythema, edema and scabbing, and slight to severe scaling. Mid-dose males had very slight edema. Skin condition observed for control and low dose rats were comparable to one another.

BODY WEIGHT MEASUREMENTS: Measured during predosing period and weekly thereafter. There were no compound related changes in body weights.

skin at 10 and 100 mg/kg (both sexes), and on mild FEP alterations in male rats at 10 and 100 mg/kg.

DATA QUALITY: Study was conducted in accordance with recognized national and international scientific procedures for determining the neurotoxicological effects of a test substance applied dermally repeatedly for 14 weeks in experimental animals. The study was conducted in compliance with GLP regulations, provides full characterization of the test material, and supports the finding of a NOAEL.

RELIABILITY:

1 w/o restriction	[X]
2 w restriction	[ ]
3 not reliable	[ ]
4 not assignable	[ ]

Reason: Followed recognized toxicology testing procedures and test material adequately characterized.

GENETIC TOXICITY

TOXICITY REPORT NUMBER: MU-17 (C_{13})

STUDY TYPE: Salmonella typhimurium/Escherichia coli Mutagenicity Assay

TEST MATERIAL: Alkyl glycidyl ether (C_{12}-C_{13}); >98% pure; clear colorless liquid.

STUDY NUMBER(S): G96BK39.502001R; Project 805-13-2

SPONSOR: The Society of the Plastics Industry, Epoxy Resin Systems C_{12}-C_{14} Task Force

TESTING FACILITY: MA BioServices, Inc., 9630 Medical Center Drive, Rockville, MD 20850.

TITLE OF REPORT: Bacterial Reverse Mutation Assay with an Independent Repeat Assay.

AUTHOR(S): V.O. Wagner and K.E. Burnett

REPORT ISSUED or STUDY COMPLETION DATE: November 10, 1997

RECOGNIZED METHOD, i.e. OECD: OECD Guideline 471 and 472.

GLP: Yes

TEST ORGANISM USED: Salmonella typhimurium strains: TA98, TA100, TA1535, and TA1537; and Escheria coli WP2 uvrA.

TEST COMPOUND CONCENTRATIONS USED: Preliminary toxicity test employed 10 doses, ranging from 6.7 to 5000 μg/plate. In the mutation assays, 6 concentrations, ranging from 10 to 5000 μg/plate, were evaluated in triplicate along with appropriate vehicle and positive controls.

CONTROL MATERIALS: The following control materials were employed.

9-aminoacridine
Sodium azide (NaN_3)
2-nitrofluorene
2-aminoanthracene
Methyl methanesulfonate

Negative control: Acetone

Positive Control:

Metabolic Non-activation:

9-aminoacridine: for TA1537 (75 μg/plate)
Sodium azide (NaN_3): for TA100, TA1535 (1.0 μg/plate)
2-nitrofluorene: for TA98 (1.0 μg/plate)
Methyl methanesulfonate: WP2 uvrA (1,000 μg/plate)

Metabolic Activation:

2-aminoanthracene: all strains (1.0 μg/plate for Salmonella strains; and 10.0 μg/plate for E. coli)

ACTIVATION: Aroclor 1254-induced rat liver S9 was prepared from male Sprague-Dawley rats induced with a single i.p. injection of Aroclor 1254 (500 mg/kg) 5 days prior to sacrifice. S9 mix was prepared immediately before its use and contained 10% S9, 5 mM G-6-P, 4 mM B-nicotinamide-adenine dinucleotide phosphate, 8mM $MgCl_2$ and 33 mM KCl in a 100 mM phosphate buffer at pH 7.4.

TEST PERFORMANCE:

o Type of Salmonella Assay

_X_ Standard plate assay
_X_ Pre-incubation (overnight)
___ "Prival" modification
___ Spot Test

PROTOCOL: Test material was plated with tester strains in the presence and absence of rat liver S9 activation. Minimal top agar, containing 0.8% agar and 0.5% NaCl was melted and supplemented with L-histidine, D-biotin and L-tryptophan. Bottom agar was Vogel-Bonner medium E. Nutrient bottom agar was Vogel-Bonner minimal medium E. Nutrient broth was Vogel-Bonner salt solution supplemented with Oxoid Nutrient Broth No. 2, 50 μL of test article, 0.5 ml of S9 or

Sham mix, 100 µL of tester strain were added to 2 mL of molten selective top agar at 45°C. Mixture was vortexed and overlaid on minimal bottom agar. After solidification, plates were inverted and incubated for 48-72 hours at 37°C. Plates were counted.

REPORT RESULTS:
Preliminary Cytotoxicity assay: Precipitate was observed at 667 µg/plate and toxicity at >333 to 3333 µg/plate with TA98, TA100 and TA1535 w/S9. Based upon these results, the maximum doses plated were 3333 µg/plate with Salmonella w/S9 and 5000 µg/plate with all other tester strain/activation combinations.

Mutation assay: Test compound induced a significant increase in the number of revertant colonies over that shown in the solvent control plates for strain TA1535 with and w/o S9 activation. No other positive responses were observed for the other tester strains. Positive controls produced the expected response in all experiments.

CONCLUSION: Test material was mutagenic in S. Typhimurium TA1535 with and w/o S9 activation.

DATA QUALITY: Study was conducted in accordance with a recognized scientific procedure for determining the adverse effects of a test substance in the Ames Salmonella and E. coli Assay following GLP regulations. Positive controls used are those recognized and required in contemporary mutagenic assays; and also confirmed the sensitivity of the test procedure. The study meets national and international scientific standards and provides sufficient information to support the conclusions regarding the mutagenic findings demonstrated from the study data.

RELIABILITY:

1 w/o restriction	[X]
2 w restriction	[ ]
3 not reliable	[ ]
4 not assignable	[ ]

Reason: Study was conducted in accordance with acceptable international test guidelines and in compliance with GLP.

TOXICITY REPORT NUMBER: MU-18 (C_{13})

STUDY TYPE: Micronucleus Cytogenetic Assay in Mice

TEST MATERIAL: Alkyl glycidyl ether (C_{12}-C_{13}); >98% pure

TESTING FACILITY: Microbiological Associates, Inc.(MA)
9630 Medical Center Drive
Rockville, MD 20850

STUDY NUMBER(S): G96BK39.122; Project No. 805-13-3

SPONSOR: The Society of the Plastics Industry, Epoxy Resin Systems C_{12}-C_{14} Task Force

TITLE OF REPORT: Micronucleus Cytogenetic Assay in Mice

AUTHOR(S): Ramadevi Gudi, PhD.

REPORT ISSUED or STUDY COMPLETION DATE: February 3, 1997

RECOGNIZED METHOD, i.e. OECD: OECD 474; EEC Directive 79/831 Annex V, B.12; EPA Health Effects Guidelines, Subpart 798.5395.

GLP: Yes

TEST ANIMAL: ICR Mice, 6-8 weeks old at initiation, males (25.5-34.7 g); females (22.1-29.5 g); housed 5/sex/cage.

TEST COMPOUND CONCENTRATIONS USED: Route of administration was intraperitoneal injection.

Dose Levels: (total volume was 20 ml)
(a) Pilot assay: 1, 10, 100, 1000 mg/kg to males only;
5000 mg/kg to males and females
Group size: 5/sex/dose

(b) Toxicity assay: 2500 or 4500 mg/kg males and females;
Group size: 5/sex/dose

(c) Micronucleus assay: 1000, 2000 or 4000 mg/kg males and females;
Group size: 15/sex/dose (except high dose which had 20/sex; replacements)

CONTROL MATERIAL: Source of all control materials was specified.

Vehicle control: Corn oil (CAS No. 8001-30-1) 20 ml/kg
Positive control: Cyclophosphamide (CP) (CAS No. 6055-19-2) 60 mg/kg

TEST PERFORMANCE:

1. Treatment and Sampling Times:

   (a) Test compound and vehicle control:
   Dosing: _X_ once or ___ twice (24 hr apart)
   Sampling (after last dose): ___ 6 hr, ___ 12 hr;
   _X_ 24 hr; _X_ 48 hr; _X_ 72 hrs

   (b) Positive control:
   Dosing: _X_ once or ___ twice (24 hr apart)
   Sampling (after last dose): ___ 6 hr, ___ 12 hr;
   _X_ 24 hr; ___ 48 hr; ___ 72 hrs

2. Tissues and Cells Examined:
   femur bone marrow;
   1000 polychromatic erythrocytes (PCEs) per animal;
   1000 normochromatic erythrocytes (NCEs) per animal;
   Ratio of PCE/total erythrocytes, per 1000 erythrocytes

3. Details of slide preparation:
   Twenty-four, 48, and 72 hrs after dose administration, 5M/5F per test and control group were sacrificed with CO_2 asphyxiation. Positive control group was sacrificed 24 hours after dosing. Immediately after sacrifice, femurs were exposed and bone marrow aspirate into a syringe containing fetal bovine serum and transferred to a centrifuge tube where the bone marrow cells were pelleted and the supernatant drawn off. Cells were resuspended by aspiration with capillary pipette, and a small drop of bone marrow suspension was spread onto a clean glass slide, air dried, fixed by dipping in methanol and stained with May-Gruenwald Giemsa.

REPORT RESULTS: Results from Pilot and Toxicity Assays provided evidence of mortality at 5000 mg/kg and 4500 mg/kg, respectively. Lethargy was evident at 1000 mg/kg and 2500 mg/kg, respectively. Based upon these results, the high dose for the micronucleus test was set at 4000 mg/kg. In the micronucleus test, no mortality was observed. The number of micronucleated PCEs per 1000 cells in test groups was not statistically increased relative to the vehicle control in either sex, regardless of collection time. The positive control (CP) induced a significant increase in micronucleated PCEs in both sexes.

CONCLUSION: The test material was negative (not clastogenic) in the micronucleus test using male and female ICR mice.

DATA QUALITY: Study was conducted in accordance with a recognized scientific procedure for determining the adverse effects of a test substance in the Mouse Micronucleus Cytogenetic Assay following GLP regulations. Positive controls used are those recognized and required in

contemporary mutagenic assays; and also confirmed the sensitivity of the test procedure to detect an increase in micronuclei in vivo. The study meets national and international scientific standards and provides sufficient information to support the conclusions regarding the absence of positive mutagenic findings demonstrated from the study data.

RELIABILITY:

1 w/o restriction	[X]
2 w restriction	[ ]
3 not reliable	[ ]
4 not assignable	[ ]

Reason: The test material was described as Alkyl Glycidyl Ether (C_{12}-C_{13}), with a purity of >98%. Study was conducted in accordance with acceptable international test guidelines and in compliance with GLP.

TOXICITY REPORT NUMBER: MU-19 (C_{13})

STUDY TYPE: In Vitro Mammalian Cell Gene Mutation Assay

TEST MATERIAL: Alkyl glycidyl ether (C_{12}-C_{13}); >98% pure; clear colorless liquid

STUDY NUMBER(S): G96BK39.782001R; 805-13-2

SPONSOR: The Society of the Plastics Industry, Epoxy Resin Systems C_{12}-C_{14} Task Force

TESTING FACILITY: MA BioServices, Inc., 9630 Medical Center Drive, Rockville, MD 20850.

TITLE OF REPORT: In Vitro Mammalian Cell Gene Mutation Test with an Independent Repeat Assay.

AUTHOR(S): Richard H.C. San and Jane J. Clarke

REPORT ISSUED or STUDY COMPLETION DATE: March 16, 1998

RECOGNIZED METHOD, i.e. OECD: OECD 476; EPA Health Effects Testing Guidelines Subpart 798.5300.

GLP: Yes

TEST CELLS USED: Chinese hamster ovary (CHO) cells, subline CHO-K_1-BH_4.

Properly maintained: Yes, in Ham's F-12 medium with newborn calf serum (5%)
Periodically checked for mycoplasm: Yes, negative
Periodically checked for karyotype stability: Yes
Periodically "cleansed" against high spontaneous background: Yes

LOCUS EXAMINED: hypoxanthine-guanine phosphoribosyl transferase locus (HGPRT).

TEST COMPOUND CONCENTRATIONS USED: 100, 250, 750, 2000, and 5000 ug/ml w/o metabolic activation; 25, 50, 75, 125 and 150 ug/ml w/S9 metabolic activation.

CONTROL MATERIALS: Manufacturer and lot number of all control materials were reported.

Ethyl Methanesulfonate (EMS)
Benzo(a)pyrene [B(a)P]
Solvent Control: Acetone
Positive Control:

Metabolic Non-activation:
EMS: 0.2 µl/ml

Metabolic Activation:
B(a)P: 4 µg/ml

ACTIVATION: Aroclor 1254-induced rat liver S9 prepared from male Sprague-Dawley rats was injected i.p. with 500 mg/kg Aroclor 1254 five days prior to sacrifice. Immediately prior to use, S9 was mixed with 10 mM $CaCl_2$, 4 mM NADP, 5 mM G-6-P, 30 mM KCl, 10 mM $MgCl_2$ and 50 mM NaP buffer, pH 8.0.

TEST PERFORMANCE:
Cytotoxicity assay: with and w/o activation at dose levels ranging from 0.5 to 5000 µg/ml. There was visible precipitate at 500 µg/ml and above. Cloning efficiency was 18% at 5000 µg/ml w/o metabolic activation, and 4% at 150 µg/ml with metabolic activation. Based upon the toxicity test results the doses selected ranged from 100-5000 µg/ml w/o activation, and 25-150 µg/ml w/S9 activation.

CHO/HGPRT Mutation Assay: Cells were seeded in F12FBS5-Hx (Ham's F12 medium w/o hypoxanthine) at a density 5 x 10^5 cells/25 cm^2 flask, and incubated at 37°C in 5% CO_2 for 18-24 hrs. Dosing solution (50 µl) was added to 5 ml F12FBS5-Hx (non-activated), or 4 ml F12FBS5-Hx plus 1 ml S9 (activated). Duplicate flasks were exposed to five concentrations of test article for 5 hours at 37°C. Afterward, cells were washed with Ca^{++} and Mg^{++} free Hanks' saline solution (CMF-HBSS) and cultured in F12FBS5-Hx for 18-24 hours at 37°C. Cells were subcultured to determine cytotoxicity and phenotypic expression. At the end of the subculture period (7-10 days), cells were trypsinized at 2-3 day intervals and subcultured independently in F12FBS5-Hx at a density of 10^6 cells/100 mm dish. At the end of the expression period, selection of mutant phenotype was

performed. Selection of TG-resistant phenotype, replicates were trypsinized and replated at a density of 2 x 10^5 cells/100 mm dish in F12FBS5-Hx containing 6-thioguanine. Cells were incubated for 7-10 days, fixed, stained and counted. The minimum mutant frequency was set at >40 mutants per 1,000,000 clonable cells.

REPORT RESULTS: Alkyl glycidyl ether did not induce mutations at the HGPRT locus in Chinese hamster ovary cells under the conditions of this method. The sensitivity of the test was demonstrated by positive results (clear increase in mutation frequency) with both EMS and B(a)P.

CONCLUSION: Alkyl glycidyl ether was not mutagenic in this test system.

DATA QUALITY: Study was conducted in accordance with a recognized scientific procedure for determining the adverse effects of a test substance in the In vitro Mammalian Cell Cytogenetic Assay (Hamster Ovary Cells/CHO) following GLP regulations. Positive controls used are those recognized and required in contemporary mutagenic assays; and also confirmed the sensitivity of the test procedure to reveal mutagenic responses in the test system. The study meets national and international scientific standards and provides sufficient information to support the conclusions regarding the absence of positive mutagenic findings demonstrated from the study data.

RELIABILITY:

1 w/o restriction	[X]
2 w restriction	[ ]
3 not reliable	[ ]
4 not assignable	[ ]

Reason: Study was conducted in accordance with acceptable international test guidelines and in compliance with GLP.

DEVELOPMENTAL TOXICITY:

TOXICITY REPORT NUMBER: DE-1 (C_{13})

STUDY TYPE: Screening Study for Developmental Toxicity via the Dermal Route

TEST MATERIAL: Alkyl Glycidyl Ether (C_{12}-C_{13}); >98% purity; clear colorless liquid; provided by Air Products and Chemicals, Inc. Allentown, PA.

STUDY NUMBER(S): WIL-284001

SPONSOR: The Society of the Plastics Industry, Epoxy Resin Systems C_{12}-C_{14} Task Force

TESTING FACILITY: WIL Research Laboratories, Ashland, OH 44805-9281

TITLE OF REPORT: A Dermal Developmental Toxicity Screening Study of Alkyl Glycidyl Ether in Rats

AUTHOR(S): C.M. Lindsey and D.G. Stump Ph.D.

REPORT ISSUED or STUDY COMPLETION DATE: August 20, 1996

RECOGNIZED METHOD, i.e. OECD: OECD 414 for Prenatal Developmental Toxicity.

GLP: Yes

SPECIES/SEX: Sprague-Dawley Crl:CD (SD) BR rat; virgin females; a sufficient number of sexually mature resident males of the same strain and source were used for mating.

AGE at Start of Test: Sexually mature females, approximately 12 weeks (minimum of 220 g).

ROUTE: Dermal; approximately 24 hours prior to test, the back of each rat was clipped free of hair.

DURATION OF TEST: All females were sacrificed on day 20 of gestation; test material was applied 6 hrs/day from gestation day 6 through 15; sites were not occluded or abraded.

DOSE LEVEL(s) and NUMBER OF DOSES: 0, 1, 10, 50, 100 and 200 mg/kg/day, applied in a volume of 1 ml/kg; doses adjusted based upon most recent individual body weight recorded prior to dosing. Oral ingestion prevented by placing an Agar collar on each animal during the 6-hour exposure period. Sites were washed with mild Ivory soap after each 6 hour exposure.

NUMBER OF ANIMALS/DOSE: Eight females per dose.

VEHICLE: Acetone.

CAGING/HOUSING: Upon arrival and until mating, all animals were housed individually. Each female was paired with a male for mating in the home cage of the male. After confirmation of mating, females were returned to an individual cage.

CAGESIDE OBSERVATIONS: Examined twice daily for general condition and behavior. All cages checked for dead or moribund animals. There were no adverse effects except at 50 mg/kg and higher in which the animals squealed at the time of dosing between day 7 and 15.

BODY WEIGHT MEASUREMENTS: Individual body weights were recorded for females on days 0, 6-16 and 20 of gestation.

FOOD CONSUMPTION/FOOD EFFICIENCY: Quantity of food consumed by each female of each group was determined on the same days as the body weights were measured.

STATISTICAL METHODS: Fetal and maternal body weights, maternal food consumption, C.L., total implants, viable fetuses, and gravid uterine weights of females were subjected to a two-tailed ANOVA, followed by Dunnett's multiple comparison. Chi-square test with Yates correction factor was used for fetal sex ratios. The number of early and late resorptions, dead fetuses and post-implantation losses were analyzed by Mann-Whitney U-test.

ORGAN WEIGHTS: Gravid uterine weights not determined.

GROSS PATHOLOGY: All animals were examined grossly for pathological changes.

FERTILITY AND REPRODUCTIVE PERFORMANCE: The following data were recorded for each group.

numbers of CL, resorptions (early and late), and viable and dead fetuses.
number of pregnant females (based upon presence of implantation sites at autopsy
implantation loss (pre- and post-); implantation sites
sex ratio
mean fetal body weights and length
litters and fetuses examined externally for malformations

FINDINGS/MEASURED ENDPOINT/INDEX (i.e. LOEL, NOAEL): There were no significant cageside observations, no effects on body weight gain or food consumption, no adverse autopsy findings and no adverse effects on the dams. Dermal irritation was observed at 50 mg/kg and greater, with fissuring, eschar formation, and atonia at 100 and 200 mg/kg. Erythema, edema and desquamation evident in a dose related manner from mild to severe. No irritation occurred at 10 mg/kg. There were no compound related effects on fertility, intrauterine growth and survival. There were no dose related effects on the number of CL, implantation sites, early or late resorptions, or on the number of dead fetuses. Necropsy: mean fetal crown-rump length, mean placenta weight, and mean fetal body weights were similar in all groups. There were no external malformations or developmental variations observed in this study, except for one control fetus with macroglossia. A NOAEL of 200 mg/kg was determined in this study for maternal toxicity and developmental toxicity. A NOAEL for dermal irritation was 10 mg/kg.

DATA QUALITY: The study was conducted in accordance with recognized scientific procedure and screening bioassay for examining the developmental effects of a test substance in developing fetuses. No internal examinations were conducted on the fetuses, and no skeletal tissues were fixed and examined to assess possible compound related effects on bone development and variations, or visceral anomalies. The study was conducted in full compliance with GLP regulations.

RELIABILITY:

1 w/o restriction	[ ]
2 w restriction	[X]
3 not reliable	[ ]
4 not assignable	[ ]

Reason: Followed recognized toxicology testing procedures in compliance with GLP regulations. However, visceral and skeletal techniques were not included in the bioassay protocol and may affect a full screen for all possible developmental effects not detected via gross observations.

CHEMICAL: Alkyl (C_{12}-C_{14}) glycidyl ether; Araldite DY 025; Epoxide 8; CAS # 68609-97-2

HEALTH EFFECTS (TOXICITY) TESTS: ROBUST SUMMARIES

ACUTE TOXICITY

REPORT NUMBER: AO-4 (E)

STUDY TYPE: Acute Oral Toxicity in Rats

TEST MATERIAL: Epoxide 8

STUDY NUMBER(S): None listed

SPONSOR: The Proctor and Gamble Company

TESTING FACILITY: Miami Valley Laboratories, The Proctor & Gamble Company

TITLE OF REPORT: Acute Oral Toxicity

AUTHOR(S): Clifford A. Ivy, Ph.D.

REPORT ISSUED or STUDY COMPLETION DATE: August 30, 1961

RECOGNIZED METHOD, i.e. OECD: Pre-dates but consistent with NAS Publication 1138 dated 1977); Thompson-Weil Moving Average Method (1947)

GLP: Not stated

SPECIES/SEX: Sprague-Dawley Rats; male/female weighing 200-250 grams.

DOSE LEVEL(S) and NUMBER OF DOSES: Four dose levels: 10.0, 14.7, 21.5 and 31.6 ml/kg.

NUMBER OF ANIMALS/DOSE: Five animals per dose; both sexes were used but the number of each sex per dose was not stated. Housed in divided cages containing 3 males and 3 females per cage.

MEASURED ENDPOINT/INDEX (i.e. LD50, PII): LD50 19.2 ml/kg (equivalent to 17.1 g/kg). Values determined by method of Thompson and Weil and 95% Confidence Limits provided.

STUDY METHOD: Five Sprague-Dawley rats per dose administered a single oral dose of the test material via gavage. Animals were fasted overnight for 18-20 hours (except for water). Animals observed for mortality, pharmacologic and/or toxicologic effects at 15, 30, 60, 120 and 240 minutes after dosing and daily thereafter for 14 days. Individual body weights were recorded prior to fasting,

at time of termination or discovery of death. Two animals/dose were subjected to gross necropsy and tissues taken for microscopic evaluation.

RESULTS/OBSERVATIONS: No observations reported other than mortality.

DATA QUALITY: Study was conducted in accordance with a recognized contemporary scientific procedure for analyzing the acute oral toxicity of a test material in experimental animals. The study protocol failed to differentiate the effects by sex, did not report cageside observations, did not report the vehicle used and did not provide an adequate analysis of the test material. Therefore, it cannot support the findings regarding the LD50 in Sprague-Dawley strain albino rats.

RELIABILITY:

1 w/o restriction	[ ]
2 w restriction	[ ]
3 not reliable	[X]
4 not assignable	[ ]

Reason: Followed recognized toxicology testing procedures, in apparent conformance with GLP record keeping (although not stated) and statistical analysis of test results. However, the test material was not fully characterized and thus it is not reliable until such information is known.

REPORT NUMBER: EI-3 (E)

STUDY TYPE: Rabbit Eye Irritation

TEST MATERIAL: Epoxide 8

STUDY NUMBER(S): None listed

SPONSOR: The Proctor and Gamble Company

TESTING FACILITY: Miami Valley Laboratories, The Proctor & Gamble Company

TITLE OF REPORT: Rabbit Eye Irritation

AUTHOR(S): Clifford A. Ivy, Ph.D.

REPORTS ISSUED or STUDY COMPLETION DATES: June 2, 1961; April 10, 1964; November 14, 1972; May 14, 1973 and May 26, 1973. NOTE: All studies were reported under one file.

RECOGNIZED METHOD, i.e. OECD: Pre-dates but consistent with NAS Publication 1138 dated 1977); Draize et al. (1959); modification of Kay and Calandra (1962).

GLP: Not stated

SPECIES/SEX: New Zealand albino rabbits, sex and weight not reported.

DOSE LEVEL(S) and NUMBER OF DOSES: 0.1 ml of undiluted test material placed in the right eye of each rabbit.

NUMBER OF ANIMALS/DOSE: Three rabbits in each group (rinsed and unrinsed).

MEASURED ENDPOINT/INDEX (i.e. LD50, PII): In separate tests reported, the range of Maximum Average Scores (MAS) for unrinsed eyes was 2.0-13.3; there was no corneal involvement and only mild conjunctivitis which cleared in 1-2 days. For rinsed eyes the MAS was 4-14.0, no corneal involvement, and mild conjunctivitis clear in 1 day.

STUDY METHOD: Test material (0.1 ml) was placed into the conjunctival sac of one eye in each of 3 rabbits. Rinsing, when used, was performed 4 seconds after instillation of test material by using tap water. Treated eyes of all animals were evaluated for irritation at 1 hour and 1, 2, 3, 4 and 7 days, then weekly for five weeks (discontinued if no irritation). Corneas were reexamined at the same time periods with 0.2% sodium fluorescein.

RESULTS/OBSERVATIONS: No corneal involvement and only mild transient conjunctivitis, clear in 1 to 2 days in rinsed and unrinsed eyes. Test material was considered minimally irritating.

DATA QUALITY: Study was conducted in accordance with a recognized scientific procedure for analyzing the primary eye irritation of a test material in experimental animals, and appeared to follow recognized GLP procedures. Although the study meets acceptable scientific protocol it does not provide sufficient chemical characterization of the test material. Therefore, it cannot support the findings regarding the potential eye irritation in New Zealand albino rabbits.

RELIABILITY:

1 w/o restriction	[ ]
2 w restriction	[ ]
3 not reliable	[X]
4 not assignable	[ ]

Reason: Followed recognized toxicology testing procedures. However, the test material was not fully characterized and thus it is not reliable until such information is known.

REPORT NUMBER: DI-5 (E)

STUDY TYPE: Rabbit Skin Irritation

TEST MATERIAL: Epoxide 8

STUDY NUMBER(S): None listed

SPONSOR: The Proctor and Gamble Company

TESTING FACILITY: Miami Valley Laboratories, The Proctor & Gamble Company

TITLE OF REPORT: Skin Irritation

AUTHOR(S): Clifford A. Ivy, Ph.D.

REPORTS ISSUED or STUDY COMPLETION DATES: August 30, 1961, April 10, 1964, December 28, 1972 and June 7, 1973. NOTE: All studies reported under one file.

RECOGNIZED METHOD, i.e. OECD: Pre-dates but consistent with NAS Publication 1138 dated 1977); Draize, et al. (1944).

GLP: Not stated

SPECIES/SEX: New Zealand albino rabbits, weighing greater than 2 kilograms; sex not stated.

DOSE LEVEL(S) and NUMBER OF DOSES: 0.5 ml of undiluted test material on abraded and unabraded skin sites.

NUMBER OF ANIMALS/DOSE: Three to six rabbits per group; each animal had an abraded and unabraded test site; both open and closed patch techniques were used.

MEASURED ENDPOINT/INDEX (i.e. LD50, PII): PII scores ranged from 3.5 to 5.7 on both open and closed patch applications. Test material was considered a moderate dermal irritant.

STUDY METHOD: Undiluted test material (0.5 ml) was applied to the shaved backs of test animals; each rabbit was further prepared by abrading an area of their back (deep enough to penetrate the horny layer of the epidermis). Separate tests evaluated occlusion and non-occlusion. The occluded sites were wrapped with gauze and occluded with clear polyethylene film for 24 hours. After 24 hours the bandages were removed and the test sites were observed for erythema and edema, and again at 72 hrs.

RESULTS/OBSERVATIONS: Erythema and edema scores were not reported, only the combined PII was presented, and there was no differentiation between abraded versus unabraded sites. Range of PII scores was 3.5-5.7 and the test material was classified a moderate dermal irritant.

DATA QUALITY: Study was conducted in accordance with a recognized scientific procedure for analyzing the primary dermal irritation of a test material in experimental animals. Although the study meets acceptable scientific protocol it does not provide sufficient chemical characterization of the test material nor does it provide adequate information regarding individual scores for erythema, edema, or abraded and unabraded data. Therefore, it cannot support the findings regarding the potential dermal irritation in New Zealand albino rabbits.

RELIABILITY:

1 w/o restriction	[ ]
2 w restriction	[ ]
3 not reliable	[X]
4 not assignable	[ ]

Reason: Followed recognized toxicology testing procedures. However, the test material was not fully characterized and is not reliable until such information is known.

REPORT NUMBER: DS-5 (E)

STUDY TYPE: Skin Sensitization in Guinea Pigs

TEST MATERIAL: Epoxide 8

STUDY NUMBER(S): None listed

SPONSOR: The Proctor and Gamble Company

TESTING FACILITY: Miami Valley Laboratories, The Proctor & Gamble Company

TITLE OF REPORT: Skin Sensitization - Guinea Pigs

AUTHOR(S): Clifford A. Ivy, Ph.D.

REPORT ISSUED or STUDY COMPLETION DATE: Undated; cover report December 18, 1973.

RECOGNIZED METHOD, i.e. OECD: Pre-dates but consistent with NAS Publication 1138 dated 1977); E.V. Buehler (1965).

GLP: Not stated

SPECIES/SEX: Albino guinea pigs; weighing 250-325 gm; sex, source and strain not stated.

DOSE LEVEL(S) and NUMBER OF DOSES: 0.5 ml of a 10% solution in diethyl phthalate.

NUMBER OF ANIMALS/DOSE: Twenty test and 10 control g. pigs.

MEASURED ENDPOINT/INDEX (i.e. Sensitization): Test material did not induce delayed contact hypersensitivity in guinea pigs.

STUDY METHOD: Tested in accordance with the Buehler Patch Test (1965) (one of several sensitization methods acceptable to OECD). Twenty animals were allocated to test groups and 10 to a vehicle control group. The diluted test material (10% in diethyl phthalate) was applied to the shaved backs of test animals for 6 hours; this was repeated 3 times weekly for 3 weeks. Two weeks after the last exposure all test and control animals were challenged in the same manner with duplicate closed patches on the left flank. Eighteen to 20 hours after removal of the patches all animals were treated with a dipilatory on the test site, rinsed and graded 3-5 hours latter.

RESULTS/OBSERVATIONS: There was no skin sensitization reaction reported for the test material.

DATA QUALITY: Study appeared to follow the protocol of Buehler, an acceptable test method for dermal sensitization. However, insufficient information was provided for the test material and for the individual details of the study, no results provided for the vehicle control, and no positive control results were reported for the lab to confirm the sensitivity of the method. Therefore, the results from this summary cannot be used to support the conclusion that the test material does not induce delayed contact hypersensitivity in guinea pigs.

RELIABILITY:

1 w/o restriction	[ ]
2 w restriction	[ ]
3 not reliable	[X]
4 not assignable	[ ]

Reason: Followed recognized toxicology testing procedures. However, the test material was not fully characterized and thus it is not reliable until such information is known.

REPORT NUMBER: DS-6 (E)

STUDY TYPE: Skin Sensitization in Humans

TEST MATERIAL: Epoxide 8

STUDY NUMBER(S): None listed

SPONSOR: The Proctor and Gamble Company

TESTING FACILITY: Miami Valley Laboratories, The Proctor & Gamble Company

TITLE OF REPORT: Skin Sensitization - Humans

AUTHOR(S): Clifford A. Ivy, Ph.D.

REPORT ISSUED or STUDY COMPLETION DATE: Undated (apparently 1962).

RECOGNIZED METHOD, i.e. OECD: Pre-dates but consistent with NAS Publication 1138 dated 1977); E.V. Buehler (1965).

GLP: Not stated

SPECIES/SEX: Only specified as human subjects; age, sex, ethnicity, etc. not provided.

DOSE LEVEL(S) and NUMBER OF DOSES: A 10% solution in diethyl phthalate.

NUMBER OF ANIMALS/DOSE: 57 human subjects.

MEASURED ENDPOINT/INDEX (i.e. Sensitization): Test material did not induce delayed contact hypersensitivity in humans.

STUDY METHOD: Tested in accordance with the Buehler Patch Test (1965) (one of several sensitization methods acceptable to OECD). Fifty-seven human subjects were given 9 insult doses of a 10% test material solution in diethyl phthalate. This was followed by a challenge dose after 14 days to the same and another exposure site.

RESULTS/OBSERVATIONS: There was no dermal sensitization reaction reported for the test material.

DATA QUALITY: Study stated that it followed the protocol of Buehler (unpublished until 1965), an acceptable test method for dermal sensitization. However, insufficient information was provided for the test material and for the individual details of the study, no results provided for the vehicle control, and no positive control results were reported for the lab to confirm the sensitivity of the method. Therefore, the results from this summary cannot be used to support the conclusion that the test material does not induce contact hypersensitivity in humans.

RELIABILITY:

1 w/o restriction	[ ]
2 w restriction	[ ]
3 not reliable	[X]
4 not assignable	[ ]

Reason: Study stated that it followed the protocol of Buehler, an acceptable test method for dermal sensitization. However, insufficient information was provided for the test material and for the individual details of the study, no results provided for the vehicle control, and no positive control results were reported for this lab to confirm the sensitivity of the method. Therefore, the results from this summary cannot be used support the conclusion that the test material does not induce delayed contact hypersensitivity in humans.

REPORT NUMBER: AD-1 (E)

STUDY TYPE: Acute Dermal Toxicity in Rabbits

TEST MATERIAL: Epoxide 8; colorless liquid; 51.6-57% C12 glycidyl ether, 18.2-20% C14 glycidyl ether, 4.1-5% C16 glycidyl ether; oxirane oxygen 5.4-6.2%; epichlorohydrin 23-25 ppm; sp. gravity 0.886 g/ml (room temp)

STUDY NUMBER(S): Project No. 3029.526

SPONSOR: The Proctor and Gamble Company

TESTING FACILITY: Springborn Institute for Bioresearch, Inc. Spencerville, OH 45887

TITLE OF REPORT: Multi-Dose Acute Percutaneous Toxicity - Rabbits

AUTHOR(S): Richard A. Hiles, Ph.D.

REPORT ISSUED or STUDY COMPLETION DATE: April 14, 1980

RECOGNIZED METHOD, i.e. OECD: Pre-dates OECD, but consistent with OECD 402.

GLP: Yes

SPECIES/SEX: Male, New Zealand White Rabbits, at least 5 months old; sexually mature.

DOSE LEVEL(S) and NUMBER OF DOSES: Three doses plus untreated control: 4.5, 1.5, 0.5, and 0 ml/kg

NUMBER OF ANIMALS/DOSE: Forty male rabbits; 10 per group.

MEASURED ENDPOINT/INDEX (i.e. mortality): There were no deaths reported after 3 days.

STUDY METHOD: Test animals' backs were clipped 3 days prior to dosing and the day of dosing; test material applied to Blenderm patch and placed securely to the back with rubberized cloth (occluded) for 24 hours; restrained. A dry patch was applied to the control group. After patch

removal, application sites rinsed with tap water for 15-30 seconds, blotted dry and after 30 minutes they were scored for irritation. Recorded again at 72 hours. Each animal was weighed prior to test and at necropsy. Immediately prior to sacrifice, blood was collected from the vena cava of each animal and checked for Hgb, Hct, WBC, RBC, and differential leukocyte. Organ weights determined for testes with and without epididymis, and for liver, heart, kidneys, and brain. The following tissues were collected for examination: testicle, epididymis, ductus deferens, seminal vesicle, prostate, and heart.

RESULTS/OBSERVATIONS: There were no deaths. Slight to moderate irritation was reported at 24 and 72 hours in treated groups, but not in control. There were no compound related effects on body weight, organ weight, blood morphology, necropsy, or histopathology (of limited organs) reported.

DATA QUALITY: Study was an expanded protocol of an acute dermal application test method, including blood morphology and histopathology of selected organs (i.e. testes, epididymis and heart). Test material was adequately characterized and the protocol was conducted in accordance with GLP procedures. The observation period was shortened from 14 days to 3 days and there was no mortality and toxicity was limited to slight/moderate dermal irritation. Test method demonstrates that no adverse effects, other than dermal irritation, were observed at the highest dose tested, 4.5 ml/kg (approx. 4 g/kg b. wt.).

RELIABILITY:

1 w/o restriction	[ ]
2 w restriction	[X]
3 not reliable	[ ]
4 not assignable	[ ]

Reason: Followed recognized toxicology testing procedures, except for a shortened observation period (3 days vs 14 days); conducted in conformance with GLP regulations; and test material was fully characterized.